THE MALONIC ESTER SYNTHESIS OF AMINO ACIDS

BY

JOSEPH FRANCIS SHEKLETON

B.S., St. Ambrose College, 1940

M.S., University of Illinois, 1941

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SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY IN THE GRADUATE SCHOOL OF THE UNIVERSITY OF ILLINOIS, 1943

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Introduction

Because of the increasing need for amino acids in nutritional and therapeutic studies it is highly desirable that more convenient syntheses of some of these substances be developed. The malonic ester synthesis, first used by Fischer[1] in 1901 and still in use today, is applicable to the preparation of many different amino acids; however, the yields obtained over the numerous steps involved in this method are low. Certain modifications of the Fischer synthesis, such as Sörensen's phthalimidomalonic ester method[2] and Curtius' malonazide acid method,[3] have been useful only for small-scale preparations. In the recent literature there are indications that conversion of alkylmalonic esters and acids to amino acids by processes involving nitrosation[4] or diazo coupling[5] followed by reduction might be much more satisfactory than Fischer's method for this transformation. There is also indication that the use of other acylaminomalonic esters[6,7,8] may be preferable to Sörensen's utilization of phthalimidomalonic ester. The present work was undertaken to evaluate and extend these newer modifications of the malonic ester method.

Discussion of Results

The action of ethyl nitrite on alkylmalonic acids and alkylmalonic esters was found to be unsatisfactory as a general method for the preparation of oximino compounds which could be converted to α-amino acids. *n*-Butylmalonic acid, *n*-amylmalonic acid, benzylmalonic acid and α-carboxy-β-(3-indole)-propionic acid were subjected to treatment with ethyl nitrite and dry hydrogen chloride, and *n*-butylmalonic ester and *n*-amylmalonic ester were treated in this way and also with ethyl nitrite in the presence of sodium methoxide. Nitrosations of these esters with nitrosyl chloride were attempted, but again no satisfactory product could be obtained.

Attempts to prepare *dl*-threonine were encouraged by the

ready availability of ∝-chloroethyl methyl ether.[9] This substance was treated with sodiomalonic ester to give a fifty-four percent yield of diethyl ∝-methoxyethylmalonate. This product, however, decomposed even under very mild conditions of saponification, and did not yield a satisfactory bromination product. Attempted nitrosation of the ∝-methoxyethylmalonic ester and its coupling with benzene diazonium choride also were unsuccessful.

The use of acetamidomalonic ester was applied to the attempted preparation of *dl*-threonine. The first condensation reaction with ∝-chloroethyl methyl ether, however, could not be effected. Other alkyl halides were condensed successfully with diethyl acetamidomalonate, leading to the isolation of *dl*-*N*-acetylphenylalanine and *dl*-*N*-acetylnorvaline in good overall yields. The *N*-acetyl derivatives of *dl*-leucine and *dl*-norleucine were also obtained, though in somewhat lower yields. Only one intermediate, the alkylacetamidomalonic ester, was isolated in this synthesis of *N*-acetylamino acids, and it required no purification. The use of secondary halides was given but little attention, and yielded no satisfactory product under the conditions necessary for condensations involving the primary halides.

A successful synthesis of *dl*-glutamic acid was devised. Diethyl acetamidomalonate and methyl acrylate were allowed to undergo a Michael condensation and the product obtained from this reaction was hydrolyzed to give a sixty-four percent yield of *dl*-glutamic acid monohydrate.

Bibliography

1. Fischer, Ber., **34**, 454 (1901)
2. Sörensen, Z. physiol. Chem., **44**, 448 (1905)
3. Curtius, J. pract., Chem., (2), **125**, 211 (1930)
4. Onishchenko, J. Gen. Chem., (U.S.S.R.), **11**, 197 (1941)
5. Feofilaktov and Vinogradova, Compt. rend. acad. sci., U.R.S.S., **24**, 759 (1939)
6. Redemann and Dunn, J. Biol. Chem., **130**, 341 (1939)
7. Cannon, Thesis, Doctor of Philosophy, University of Illinois, (1943)
8. Smith, Thesis, Doctor of Philosophy, University of Illinois, (1943)
9. Swallen and Boord, J. Am. Chem. Soc., **52**, 651 (1930)

VITA

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